A new method for the preparation of 1,2-benzisoxazole-3-carboxaldehyde

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Synthesis of 1,2-benzisoxazole-3-carboxaldehyde is achieved from 3-methyl 1,2-benzisoxazole via 3-ethoxymethyl-1,2-benzisoxazole (**4**).

Keywords: 1,2-benzisoxazoles, benzylic bromination, indoxazenes

There are various 3-substituted 1,2-benzisoxazoles known in the literature for their biological activity.[1] However, a convenient synthesis of 1,2-benzisoxazole-3-carboxaldehyde (**1**) has not yet been reported. Yoshida *et al.*[2] reported its preparation from 3-arylsulfinyliminomethyl-1,2-benzisoxazole and (1,2-benzisoxazol-3-yl)methyl phenyl sulfoxide. In continuation of our work in the synthesis of new entities for anti-inflammatory agents we needed to develop a convenient method for the preparation of 1,2-benzisoxazole-3-carboxaldehyde derivatives from 3-methyl-1,2-benzisoxazole which is easily made by reported procedures.[3,4]

Here we report a simple and convenient method for the preparation of 1,2-benzisoxazole-3-carboxaldehyde (**1**) from 3-methyl-1,2-benzisoxazole (**2**) via 3-ethoxymethyl-1, 2-benzisoxazole (**4**) (Scheme 1).

We made various attempts to oxidise 3-methyl-1, 2-benzisoxazole (**2**) to the aldehyde (**1**) in one step (Table 1); unfortunately, all attempts were unsuccessful. It was then planned to convert 3-methyl-1,2-benzisoxazole (**2**) into 3-bromomethyl-1,2-benzisoxazole (**3a**) followed by oxidation to 1,2-benzisoxazole-3-carboxaldehyde (**1**). Attempts to convert 3-bromomethyl-1,2-benzisoxazole (**3a**) into 1,2-benzisoxazole-3-carboxaldehyde (**1**), and to hydrolyse 3-bromomethyl-1,2-benzisoxazole (**3a**) to **5** directly, were also unsuccessful (Table 1).

Final success was achieved by converting 3-bromomethyl-1,2-benzisoxazole (**3a**) into the 3-ethoxymethyl compound (**4**) followed by ether cleavage to 3-hydroxymethyl-1,2-benzisoxazole (**5**) which could easily be oxidised to the required carboxaldehyde (**1**).

Bromination of 3-methyl-1,2-benzisoxazole (**2**) with *N*-bromosuccinimide gave a mixture of 3-bromomethyl-1, 2-benzisoxazole (**3a**) and the dibromomethyl compound (**3b**). The ^{1}H NMR spectra of these compounds were in agreement with the assigned structures.

When 3-bromomethyl-1,2-benzisoxazole (**3a**) was treated with 1.1 equivalent of sodium metal in ethanol followed by heating at reflux for 1 h, 3-ethoxymethyl-1,2-benzisoxazole (**4**) was formed in 81% yield. 3-Ethoxymethyl-1, 2-benzisoxazole (**4**) on treatment with BBr_3 gave in 71% yield 3-hydroxymethyl-1,2-benzisoxazole (**5**) which on PDC oxidation gave 1,2-benzisoxazole-3-carboxaldehyde (**1**) in 72% yield as shown in Scheme 1.

Recently, Li *et al.*[5] reported the conversion of dihalomethyl arenes to aromatic aldehydes in excellent yields by heating in dimethyl sulfoxide. Unfortunately, in our hands 3-dibromomethyl-1,2-benzisoxazole (**3b**) remained unchanged on heating with DMSO.

In conclusion: a simple and convenient method is reported for the preparation of 1,2-benzisoxazole-3-carboxaldehyde (**1**) from 3-methyl-1,2-benzisoxazole (**2**). This method can be explored for the preparation of differently substituted 1,2-benzisoxazole-3-carboxaldehydes.

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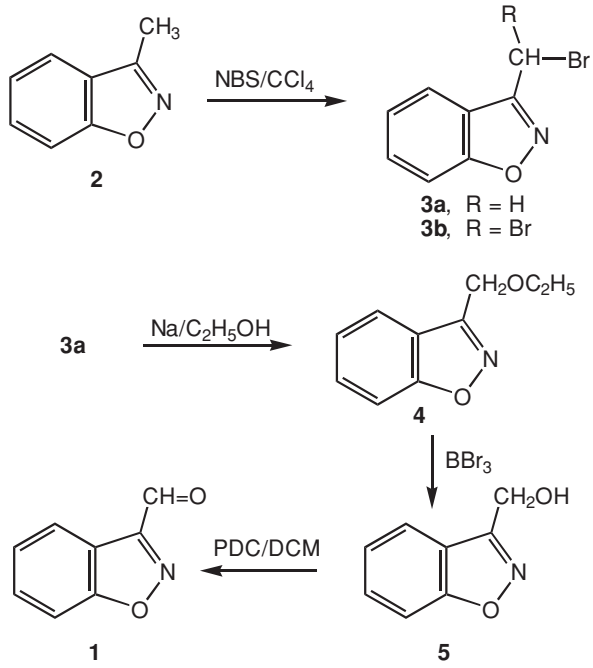
Table 1 Treatment of 3-methyl-1,2-benzisoxazole (**2**), 3-bromomethyl-1,2-benzisoxazole (**3a**), and 3-dibromomethyl-1,2-benzisoxazole (**3b**), with various reagents[a]

Substrate	Reagents / conditions
2	(a) Co acetate/NaBr, H_2O_2, sodium perborate[6] (b) PDC/celite/DCM/room temp[7] (c) SeO_2/acetic acid or C_2H_5OH[8] (d) CrO_3/H_2SO_4/acetone[9] (e) ceric ammonium nitrate/acetic acid[10]
3a	(a) $NaIO_4$/DMF, 150 °C[11] (b) DMSO, 160 °C[12] (c) DMSO/KI/Na_2CO_3, 120 °C[13] (d) DMSO/$NaHCO_3$/130 °C[14] (e) I_2/DMSO/140 °C[15] (f) KOH/isopropanol
3b	(a) DMSO/heat[5]

[a]In no case was any reaction observed; starting material was recovered.



Scheme 1

Experimental

NMR spectra were recorded in $CDCl_3$ solutions on Bruker 200 MHz (AC 200) and 300 MHz (MSL 300) instruments. Elemental analyses were performed using a Thermofinnigan CHNS analyser, Flash EA 1112 series. Melting points were recorded on a Buchi B 540 melting point apparatus and mass spectra were recorded on a GCMS-QP 5050A Shimadzu GC MS instrument. 3-Methyl-1,2-benzisoxazole was prepared by a reported procedure[3] from *o*-hydroxyacetophenone.

3-Bromomethyl-1,2-benzisoxazole (**3a**) *and 3-dibromomethyl-1,2-benzisoxazole* (**3b**): 3-Methyl-1,2-benzisoxazole (**2,** 5 g, 37.5 mmol) was placed in a two-necked round bottom flask containing carbon tetrachloride (200 ml) equipped with reflux condenser. NBS (20.06 g, 112.0 mmol) and catalytic amount of AIBN (10 mg) were added. The reaction mixture was refluxed for 3 hours under inert atmosphere in presence of light. The progress of the reaction was monitored by TLC. After completion of the reaction the reaction mixture was cooled and filtered through celite. The filtrate was concentrated under reduced pressure to obtain crude 3-bromomethyl-1,2-benzisoxazole (7.5 g). The crude product was purified by column chromatography using silica gel 60-120, eluting with petroleum ether and ethyl acetate to yield the faster-moving **3b** (1.32 g, 4.5 mmol, 20%) and slower-moving **3a** (4.86 g, 23 mmol, 61%).

3a: solid, m.p. 63 °C. ^{1}H NMR: $CDCl_3$ 4.73 (s, 2H), 7.37 (m, 1H), 7.59 (m, 2H), 7.82 (d, 1H).

3b: solid, m.p. 48 °C. ^{1}H NMR: $CDCl_3$ 6.96 (s, 1H), 7.45 (m, 1H), 7.62 (m, 2H), 8.12 (d, 1H).

3-Ethoxymethyl-1,2-benzisoxazole (**4**): 3-Bromomethyl-1, 2-benzisoxazole (**3a**) (400 mg, 1.89 mmol) was dissolved in absolute ethanol (8 ml) in a round bottom flask. Freshly cut sodium (87 mg, 3.79 mmol) was added. The reaction mixture was stirred at room temperature until effervescence ceased and then it was refluxed at 80 °C under nitrogen for 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction the mixture was concentrated under reduced pressure and then extracted with ethyl acetate (3 × 5 ml). The combined ethyl acetate layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure, to yield 3-ethoxymethyl-1,2-benzisoxazole (**4,** 280 mg, 81%) as a yellowish liquid. MS: *m/z* 177 (M^+). ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3H), 3.60 (q, 2H), 4.91 (s, 2H), 7.31 (m, 1H), 7.56 (m, 2H), 7.87 (d, 1H). Anal. calc for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found C, 67.31; H, 5.92; N, 7.49 %.

3-Hydroxymethyl-1,2-benzisoxazole (**5**): 3-Ethoxymethyl 1, 2-benzisoxazole (**4**, 100 mg, 0.56 mmol) was dissolved in dichloromethane (5 ml) in a two-neck round bottom flask equipped with rubber septum and a nitrogen balloon. The reaction mixture was cooled to –78 °C and boron tribromide in dichloromethane (280 mg, 1.12 mmol) was added to the reaction mixture. The reaction mixture was stirred overnight at -78 °C. The progress of the reaction was monitored by TLC analysis. After completion of the reaction the excess of boron tribromide was neutralised with saturated aqueous sodium hydrogen carbonate (10 ml) and then extracted with dichloromethane (3 × 5 ml). The combined dichloromethane layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure to leave 3-hydroxymethyl-1,2-benzisoxazole (**5**, 59.6 mg, 71%), solid, m.p. 67 °C; IR ($CHCl_3$): 3338, 2873, 1496, 1454, 1208, 1079, 1037, 1021, 735, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.10 (s, 2H), 7.34 (m, 1H), 7.57 (d, 2H), 7.8 (d, 1H). ^{13}C NMR: 56.7 (CH_2), 109.8 (C-7), 120.4 (C-3a), 121.8 (C-5), 123.6 (C-4), 130.1 (C-6), 157.8 (C-3), 163.2 (C-7a). Anal. Calc for $C_8H_7NO_2$ (149.15): C, 64.42; H, 4.73; N, 9.39. Found C, 64.11; H, 5.12; N, 8.92 %.

1,2-Benzisoxazole-3-carboxaldehyde (**1**): Pyridinium dichromate (0.76 g, 2.0 mmol) was added to 3-hydroxymethyl-1,2-benzisoxazole (**5**, 100 mg, 0.671 mmol) in dichloromethane (5 ml) and the mixture was stirred under inert atmosphere at room temperature for 3 h. Progress of the reaction was monitored by TLC analysis. After completion of the reaction, the mixture was filtered through celite. The filtrate was washed with water (5 ml) and then with brine (2 × 2.5 ml). The dichloromethane layer was dried over sodium sulfate and concentrated under reduced pressure to obtain 1,2-benzisoxazole-3-carboxaldehyde (**1**, 71 mg, 72%). Solid m.p. 61 °C (Lit[2] m.p. 64–65 °C). ^{1}H NMR: δ 7.48 (m, 1H), 7.68 (m, 2H), 8.20 (d, 1H), 10.43 (s, 1H).

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